GENERIC PHARMACEUTICAL INDUSTRY ASSOCIATION

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Alice E. Till, Ph.D.
President

June 1, 2000

Documents Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: [Docket No. 93D-0139] International Conference on Harmonization; Draft Revised Guidance on Q1A(R) Stability Testing of New Drug Substances and Products

Dear Madam or Sir:

The Generic Pharmaceutical Industry Association (GPIA) is pleased to have the opportunity to comment on the International Conference on Harmonization; *Draft Revised Guidance on Q1A(R) Stability Testing of New Drug Substances and Products*, which was published in the *Federal Register* on April 21, 2000.

GPIA is comprised of the manufacturers and distributors of generic medicines, as well as the providers of technical services and goods to these firms. Many members will be directly impacted by implementation of the subject draft guidance. We, therefore, submit the following comments to you for consideration as you finalize the guidance.

Positive Observations

1. The Drug Substance stress testing section (page 21448) clearly makes the connection that this testing can be used to cover distribution excursions.

2. The changing of accelerated test points (page 21448) from 0, 2, 4, 6 months to 0, 3, 6 months is appreciated. This provides an opportunity to link SUPAC changes requiring 3 months accelerated testing directly to the original NDA batch data.

3. The removal of the requirement to follow the same protocol regardless of process is definitely good (page 21449). This removes the obligation to perform accelerated studies for post-approval batches. This is equally positive for the Drug Product section.

4. The addition of a table (page 21451) to provide relative humidity ratios is positive and will be helpful for the extrapolation of data from one condition to other conditions. However, the temperatures should clearly be linked with the listed relative humidity values in the table.

5. The discussion of stability storage excursions (page 21453) is definitely a positive.

Concerns

1. Under the section, Drug Products Intended for Storage in a Refrigerator (page 21449), the following statement is made: "If significant change occurs within the first 3 months' testing at the accelerated storage condition, data should be supplied to cover use of the drug product outside of the label storage condition." This statement is vague and does not indicate the type of data to be supplied or the impact on product shipping or labeling. Is there any value in defining a specific time period where significant change is somehow unacceptable without direction for the next step? Products stored at room temperature have a defined intermediate condition that refrigerated products do not have.

2. In the next section (page 21449), Drug Products Intended for Storage in a Freezer, the following statement is made: "In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, data from elevated temperature (e.g. 5°C ±3°C or 25°C ± 2°C) on a single batch should be conducted to support use of the drug product outside of the proposed label storage condition." This statement is also vague and does not indicate which choice of conditions or the length of data to be supplied. Is there any value in defining that some additional data must be provided without defining what data is necessary? Products stored at room temperature have defined accelerated and intermediate conditions that freezer products do not have.

3. The middle column on page 21450 (Drug Product) provides discussion of application of acceptance criteria to the release limits (where applicable). This is not applicable for a pending new dosage form for which little data has been generated. The release limits should be generated on the validation batches and should be tentative and not tied to an official registration document which will then fall under the prior approval criteria for making changes to specifications in the future. The shelf life limits should be "influenced" by the levels seen within the stability programs (of batches deemed equivalent to the clinical batches).

4. Very minor grammatical observation on page 214450: ". . labeling statements ARE unacceptable. ." This occurs in both sections.

5. The intermediate storage condition for products packaged in semi-permeable containers (page 21451) should reflect the long-term condition for RH (e.g. it should be 30C/40%RH not 60%RH). The science behind the low humidity is to show that the product is stable when low amounts of water can evaporate through the package. It serves no useful scientific purpose to reduce the long-term and accelerated RH requirements and leave the intermediate the same.

6. In the glossary mention is made for the first time that results from accelerated testing are not always predictive of physical changes. It would be helpful if this comment is included in the general text and also if some regulatory expectations are added for the situations when the physical changes are observed.

Thank you.

Sincerely,

Alice E. Till, Ph.D.
President

CC J. James, Chair GPIA Stability Taskforce

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